Cutaneous Vasoconstriction affects near-infrared spectroscopy determined cerebral oxygen saturation during administration of norepinephrine

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Abstract: BACKGROUND: Perioperative optimization of spatially resolved near-infrared spectroscopy determined cerebral frontal lobe oxygenation (sco2) may reduce postoperative morbidity. Norepinephrine is routinely administered to maintain cerebral perfusion pressure and, thereby, cerebral blood flow, but norepinephrine reduces the sco2. We hypothesized that norepinephrine-induced reduction in sco2 is influenced by cutaneous vasoconstriction METHODS: Fifteen healthy male subjects (25 ± 5 yr, mean ± SD) were studied during: hyperventilation (1.5 kPa end-tidal Pco2 reduction), whole-body heating, administration of norepinephrine (0.15 g · kg · min; with and without end-tidal carbon dioxide correction), and hypoxia (FiO2: 0.12%). Arterial (sao2), skin, and internal jugular venous oxygen saturations (sjo2) were recorded, and the average cerebral capillary oxygen saturation (scapo2) was calculated. RESULTS: This study indicates that sco2 is influenced by skin oxygen saturation because whole-body heating increased sco2 by 3.6% (2.1-5.1%; 95% CI) and skin oxygen saturation by 3.1% (1.3-4.9%), whereas scapo2 remained unaffected. Conversely, hyperventilation decreased sco2 by 2.1% (0.4-3.7%) and scapo2 by 5.3% (3.8-6.9%), whereas skin oxygen saturation increased 1.8% (0.5-3.1%). In response to hypoxia, sco2 (10.2%; 6.6-13.7%), scapo2 (7.9%; 6.4-9.4%), and skin oxygen saturation (8.9%; 6.3-11.6%) all decreased. With administration of norepinephrine there was a 2.2% (1.0-4.3%) decrease in skin oxygen saturation and sco2 decreased 6.2% (4.2-8.0%), with scapo2 remaining unaffected CONCLUSION: The results confirm that spatially resolved near-infrared spectroscopy detects cerebral deoxygenation with systemic hypoxic exposure and hyperventilation. However, a commonly used vasopressor norepinephrine disturbs skin oxygen saturation to an extent that influences sco2.

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Cutaneous Vasoconstriction Affects Near-infrared Spectroscopy Determined Cerebral Oxygen Saturation during Administration of Norepinephrine

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ABSTRACT

Background: Perioperative optimization of spatially resolved near-infrared spectroscopy determined cerebral frontal lobe oxygenation (scO_2) may reduce postoperative morbidity. Norepinephrine is routinely administered to maintain cerebral perfusion pressure and, thereby, cerebral blood flow, but norepinephrine reduces the scO_2. We hypothesized that norepinephrine-induced reduction in scO_2 is influenced by cutaneous vasoconstriction.

Methods: Fifteen healthy male subjects (25 ± 5 yr, mean ± SD) were studied during: hyperventilation (1.5 kPa end-tidal PcO_2 reduction), whole-body heating, administration of norepinephrine (0.15 $\mu g \cdot kg^{-1} \cdot min^{-1}$; with and without end-tidal carbon dioxide correction), and hypoxia (FiO_2: 0.12%). Arterial (saO_2), skin, and internal jugular venous oxygen saturations (sjO_2) were recorded, and the average cerebral capillary oxygen saturation ($s_{cap}O_2$) was calculated.

Results: This study indicates that scO_2 is influenced by skin oxygen saturation because whole-body heating increased scO_2 by 3.6% (2.1–5.1%; 95% CI) and skin oxygen saturation by 3.1% (1.3–4.9%), whereas $s_{cap}O_2$ remained unaffected. Conversely, hyperventilation decreased scO_2 by 2.1% (0.4–3.7%) and $s_{cap}O_2$ by 5.3% (3.8–6.9%), whereas skin oxygen saturation increased 1.8% (0.5–3.1%). In response to hypoxia, scO_2 (10.2%; 6.6–13.7%), $s_{cap}O_2$ (7.9%; 6.4–9.4%), and skin oxygen saturation (8.9%; 6.3–11.6%) all decreased. With administration of norepinephrine there was a 2.2% (1.0–4.3%) decrease in skin oxygen saturation and scO_2 decreased 6.2% (4.2–8.0%), with $s_{cap}O_2$ remaining unaffected.

Conclusion: The results confirm that spatially resolved near-infrared spectroscopy detects cerebral deoxygenation with systemic hypoxic exposure and hyperventilation. However, a commonly used vasopressor norepinephrine disturbs skin oxygen saturation to an extent that influences scO_2.

What We Already Know about This Topic

- Cerebral oximetry by spatially resolved near-infrared spectroscopy is used to monitor and optimize cerebral oxygenation during procedures that might impair cerebral perfusion
- Changes in cutaneous perfusion could interfere with the accuracy of cerebral oximetry

What This Article Tells Us That Is New

- The effects of hypocapnia, hyperthermia, hypoxia, and norepinephrine on cerebral and forehead skin blood flow and oxygenation were studied in human volunteers
- Cerebral oximetry accurately detected cerebral deoxygenation produced by hypoxia and hyperventilation, but hyperthermia and norepinephrine affected skin oxygenation and directionally influenced cerebral oximetry readings

IT is crucial to maintain cerebral blood flow (CBF) during anesthesia, but it is difficult to determine CBF in clinical settings. On the other hand, it is straightforward to monitor frontal lobe oxygenation (scO_2) by noninvasive near-infrared spectroscopy (NIRS) that provides real-time assessment and is reported to monitor scO_2 correctly.[1] Thus, perioperative optimization may be directed to preserve scO_2 [2] and maintained scO_2 secures rapid postoperative recovery in both cardiac[3] and elderly patients.[4] For example, vasopressors are administered to prevent reductions in mean arterial pressure (MAP) that could affect CBF and in turn scO_2. However, vasopressors appear to affect scO_2 differently. Phenylephrine reduces scO_2 in anesthetized patients,[5] but that is not the case

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for ephedrine.[6] In healthy subjects the administration of norepinephrine reduces scO_2[7] with a concomitant reduction in blood flow velocity in the middle cerebral artery (MCA v_{mean}) and internal jugular venous saturation (sjO_2), suggesting that sympathetically mediated cerebral vasoconstriction reduces CBF to an extent that affects scO_2. But sympathetic innervation of the cerebral vasculature remains controversial, and whether administration of norepinephrine reduces MCA v_{mean} remains debated.[8] Alternatively, the reduction in s_cO_2 following administration of norepinephrine is influenced by cutaneous vasoconstriction.[9] Also both CBF and scO_2 are sensitive to changes in $PaCO_2$[10,11] and an increase in ventilation provoked by administration of norepinephrine could contribute to the reduction in scO_2.[12]

An influence from skin oxygenation to the NIRS signal has been identified.[13,14] In a hot environment, skin blood flow (SBF) increases, especially over the forehead,[15] whereas there is no change in CBF or muscle blood flow. However, the NIRS-determined muscle oxygenation increases during whole-body heating.[13] For evaluation of cerebral oxygen saturation in a hot environment, it appears important that hyperthermia elicits a hyperventilation-induced lowering of $PaCO_2$[16,17] and, in turn, CBF.[18] Thus, when scO_2 is unaffected by hyperthermia[19] while the internal jugular venous-derived cerebral oxygenation is reduced,[20] the maintained scO_2 indicates that scO_2 is influenced by SBF, and this hypothesis was tested in the present study. For this purpose we assessed cerebral perfusion and oxygenation while $PaCO_2$ and PaO_2 were manipulated with separate assessment of SBF and skin hemoglobin and oxygenation.

Materials and Methods

Fifteen healthy males (age 25 ± 5 yr [mean ± SD], height 182 ± 7 cm, and mass 76 ± 8 kg) participated in the study. The study was approved by the local ethics committee (H-4–2010–132, Copenhagen, Denmark) in accordance with Declaration of Helsinki including oral and written informed consent.

After arrival to the laboratory at 8:00 AM, the subjects were resting supine for 20 min before catheterization. Under local anesthesia (2% lidocaine), a catheter (Edwards Life Sciences, Irvine, CA) was inserted retrograde in the right internal jugular vein by Seldinger technique guided by ultrasound, and the tip of the catheter was placed at its bulb. The position of the catheter at the jugular bulb was verified during placement if the subjects reported a slight pain behind the ear. The placement was also confirmed by quick infusion of saline if the subject experienced an auditory response.[21,22] A 20 G catheter was placed in the brachial (n = 12) or radial artery (n = 3) of the nondominant arm and a central venous catheter (Cavafix MT134, Braun, Melsungen, Germany) was advanced through an arm vein. Catheters were connected to transducers (Edwards Life Sciences) placed at the level of the heart (fourth intercostal space; Dialogue-2000; IBC-Danica Electronic, Copenhagen, Denmark) to monitor MAP and heart rate. Data were analog-digital converted and sampled at 200 Hz (DI-720; Dataq Instruments Inc., Akron, OH) by computer software (Windaq; Dataq Instruments Inc.).

To assess scO_2 we used a spatially resolved NIRS (INVOS; Somanetics, Troy, MI), meaning that it records differences in absorption of photons returning from deep and superficial tissues[23] using light at 703 and 808 nm and an emitter-detector separation of 3 and 4 cm with the depth sensitivity corresponding to approximately one-third of the emitter-detector separation.[24] Although the algorithm of the instrument is not disclosed, the apparatus is widely used in clinical cerebral monitoring[2,3,10,25] and evaluation of its performance is therefore important. The general approach of this instrumentation is that by analyzing the signals from the two emitter-detector separations, the signal of superficial tissue layers is suppressed, providing an estimate of deep tissue, *e.g.*, the frontal lobe oxygenation. We assumed that frontal lobe activation was unchanged throughout the protocol and therefore did not influence cerebral metabolic rate of oxygen and, in turn, the NIRS signal. To avoid any influences from the frontal or sagittal sinuses to the NIRS signal, the sensor was placed high on the forehead in randomized and balanced order. The SBF was monitored by LDF (moorVMS-LDF; Moor Instruments, Axminster, United Kingdom) using light at 785 nm. The LDF sensor was integrated with a tissue oxygenation sensor (moorVMS-OXY; Moor Instruments) that uses white light spectroscopy (wavelength range, 400–700 nm) to assess skin oxygen saturation, skin hemoglobin concentrations, and temperature. The instrument self-calibrates when turned on prior and LDF and white light spectroscopy are established as valid measurements of the microcirculation of the skin.[26,27] We assumed that changes in SBF beneath the LDF sensor reflected that beneath the NIRS sensor, with the two sensors placed ipsilateral and distanced 3 to 4 cm apart.

To evaluate whether the interventions affected CBF, MCA v_{mean} was determined by transcranial Doppler sonography (2 MHz probe, Multi-Dop, DWL, Singen, Germany). Using adhesive ultrasound gel, the best signal-to-noise ratio was obtained at the temporal insonation window. Placement of the probe was randomized and balanced across subjects with respect to hemisphere, and eight subjects had the probe placed on the right side. Previous reports exclude influence of $PaCO_2$ on the diameter of the MCA and we, therefore, assumed that changes in MCA v_{mean} reflect those in CBF.[28]

Transcranial Doppler, SBF, NIRS, and skin oxygenation in addition to the blood pressure signals were all analog-digital converted and sampled on the DI-720. Following recording, values were averaged over at least 30 s before entering the statistical analysis.

Arterial and jugular venous blood samples were obtained simultaneously in preheparinised syringes. Atmospheric air was immediately removed from the syringe. The samples were analyzed for PaO_2 and $PaCO_2$, oxygen saturation (saO_2; sjO_2), and total hemoglobin (ABL700; Radiometer, Copen-

hagen, Denmark). To express the oxygen content in the arterial or venous blood, $CO_2 = 0.0031 \cdot PO_2 + Hb \cdot SO_2$ was used. The arterial to venous difference (av_dO_2) for the brain was calculated. With the assumption that $CMRO_2$ was constant, changes in CBF were calculated using the Fick equation,

$$\Delta CBF_{FICK} = \Delta \frac{1}{av_dO_2}.$$

The cerebrovascular resistance index was calculated as MAP divided by $MCAv_{mean}$ and the skin vascular resistance index was MAP divided by SBF. Using a simplified equation, $s_{cap}O_2$ was calculated:[1,29]

$$s_{cap}O_2 = \frac{s_aO_2 + s_jO_2}{2}.$$

The calculation of $s_{cap}O_2$ is based on the cerebral oxygen extraction and motivated by the assumption that oxygen extraction remains constant along the capillary network.[30,31] Gas is exchanged linearly along the entire vascular pathway from the arteries to the veins.[32,33] Thus, it can be assumed that sO_2 decreases linearly from the arterial to the venous end of the capillary and average cerebral oxygen saturation is then the midway point between arterial and venous saturations.[29]

Protocol

Following catheterization, the subjects rested supine for 30 min with elevated head rest with room temperature kept constant (22–24°C). The experiment included three trials performed in randomized and balanced order, followed by a hypoxic trial. Before each trial resting values were obtained with 43 ± 14 min rest between the trials. The trials included the following.

(1) The subjects were asked to hyperventilate to reduce the end-tidal pressure of carbon dioxide ($PETCO_2$; INNOCOR, Odense, Denmark) by 1.5 kPa. Blood samples were collected after 7 ± 2 min reflecting when the targeted $PETCO_2$ was established.

(2) To increase skin temperature, the subjects were exposed to whole-body heating. The subjects were covered with a heat-isolating aluminum blanket together with a dedicated heating blanket (Bair Hugger 505; Arizant Healthcare, Eden Prairie, MN) that was inflated by air at 42°C. Linens covered and isolated the head. Blood samples were obtained after 26 ± 7 min, reflecting when there was no further increase in SBF (skin temperature increased by 1.7 ± 0.7°C) and it was confirmed that $PaCO_2$ remained stable.

(3) Norepinephrine (0.15 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was infused through the central venous catheter for 15 min; blood samples were collected afterward. To avoid potential effects of norepinephrine on $PaCO_2$,[7] the subjects were instructed to restrain the ventilatory depth for 11 ± 5 min in order to maintain the arterial carbon dioxide. If the subject was not able to control $PETCO_2$ in this way, a tube was added to the inspired gas mixture and thus increased the ventilatory death space. Administration of norepinephrine with and without $PETCO_2$ correction was performed in randomized order.

(4) After these trials, the subjects were exposed to hypoxia (F_iO_2: 0.12%) for which the inspired air was balanced by N_2 (Altitrainer, SMTEC, Nyon, Switzerland) for 10 min, while blood samples were collected.

Statistical Methods

Based on similar studies,[7,8,34] a sample size of 15 subjects was assumed to provide $\beta < 0.20$. One-way ANOVA followed by a Tukey *post hoc* test on repeated measures evaluated variables. To express relationships between variables we used Pearson's correlation. The results are presented as changes from baseline and variables are provided with their 95% CI. We performed a two-tailed hypothesis testing and the statistically significant level was set to $P < 0.05$ with data analyzed in SAS 9.2 (SAS Institute Inc., Cary, NC). Because of insufficient signal quality, MCV v_{mean} was excluded in one subject during hyperventilation and in another subject during the control before whole-body heating. Similarly, scO_2 was excluded in one subject during whole-body heating.

Results

Hyperventilation

As intended, hyperventilation induced a 1.1 kPa decrease in $PaCO_2$ whereas PaO_2 increased (table 1). Skin oxygen saturation increased by 1.8% (0.5% to 3.1%), although there were no changes in skin hemoglobin concentrations, skin vascular resistance index, or SBF.

There were no changes in MAP, but MCA v_{mean}, sjO_2, and CBF_{Fick} all decreased. Also, the NIRS-determined scO_2 was reduced by 2.1% (0.4–3.7%; fig. 1) and $s_{cap}O_2$ was reduced by 5.3% (3.8–6.9%).

Whole-body Heating

With exposure to whole-body heating there was an increase in skin temperature by 1.6°C (0.7–2.6°C) (table 2) and a concomitant increase in SBF by 23.5 AU (10.4–36.6) and skin oxygen saturation by 3.1% (1.3–4.9%).

We did not observe any changes in MAP, MCA v_{mean}, sjO_2, or CBF_{Fick} in response to whole-body heating (table 1). Yet, there was an increase by 3.6% (2.1–5.1%; fig. 1) in scO_2, whereas $s_{cap}O_2$ remained unchanged.

Administration of Norepinephrine

With administration of norepinephrine, skin vascular resistance index increased while total hemoglobin of the skin decreased (table 2). Thus, skin oxygen saturation was reduced by 2.2% (1.0–4.3%).

Administration of norepinephrine induced in average 22 mmHg increase in MAP, whereas MCA v_{mean}, sjO_2, and CBF_{Fick} were unaffected. Yet, the scO_2 was reduced by 6.2% (4.2–8.0%; fig. 2), although $s_{cap}O_2$ remained unchanged.

Table 1. Systemic and Cerebral Hemodynamics

Units of Measure	sa_{O_2} %	sc_{O_2} %	$s_{cap}O_2$ %	sj_{O_2} %	Pa_{O_2} kPa	Pa_{CO_2} kPa	CVRi mmHg · cm^{-1} · s^{-1}	MCA v_{mean} cm/s	CBF_{Fick} AU	MAP mmHg
Control	98.3 ± 0.4	77.5 ± 5.4	81.4 ± 2.5	64.4 ± 4.8	13.7 ± 0.9	5.4 ± 0.3	2.0 ± 0.7	57.0 ± 16.6	32 ± 5	102.0 ± 10.9
NE	98.8 ± 0.3†	72.4 ± 7.3‡	81.1 ± 3.3	63.4 ± 6.5	14.5 ± 0.7†	5.0 ± 0.3‡	2.4 ± 0.8*	55.7 ± 14.7	28 ± 5*	123.2 ± 13.6‡
NE + CO_2	98.3 ± 0.6	74.0 ± 5.9†	83.4 ± 3.7	68.4 ± 7.7	13.7 ± 1.0	5.4 ± 0.3	2.2 ± 0.8	62.9 ± 20.7*	38 ± 2	122.8 ± 11.6‡
Hyperventilation	99.2 ± 0.4‡	76.1 ± 6.8*	76.4 ± 4.8‡	53.6 ± 9.8‡	15.9 ± 1.4‡	4.4 ± 0.7‡	2.3 ± 0.6*	48.1 ± 11.1†	25 ± 1‡	102.6 ± 9.1
WBH	98.4 ± 0.4*	80.0 ± 5.1†	81.9 ± 4.0	65.3 ± 7.9	14.0 ± 0.7*	5.4 ± 0.2	2.0 ± 0.9	56.0 ± 16.2	34 ± 1	102.0 ± 20.6
Hypoxia	91.8 ± 3.7‡	68.0 ± 10.7‡	73.1 ± 3.7‡	54.0 ± 4.5‡	8.7 ± 2.6‡	4.7 ± 0.4*	1.8 ± 0.5	54.8 ± 12.3	29 ± 3	91.1 ± 14.9*

Systemic and cerebral hemodynamics with hyperventilation, whole-body heating, hypoxia (f_iO_2 = 0.12%), and administration of norepinephrine (0.15 $\mu g \cdot kg^{-1} \cdot min^{-1}$) with and without P_{ETCO_2} correction.

* $P < 0.05$. † $P < 0.01$. ‡ $P < 0.001$.

CBF = cerebral blood flow; CVRi = cerebrovascular resistance index; MAP = mean arterial pressure; MCA v_{mean} = mean velocity of the middle cerebral artery; NE = administration of norepinephrine; NE + CO_2 = administration of norepinephrine with P_{ETCO_2} correction; sa_{O_2} = arterial oxygen saturation; $s_{cap}O_2$ = calculated average cerebral oxygen saturation; sc_{O_2} = NIRS-derived cerebral oxygen saturation; sj_{O_2} = internal jugular venous oxygen saturation; WBH = whole-body heating.

Administration of Norepinephrine with P_{ETCO_2} Correction

The subjects managed to keep Pa_{CO_2} at the level established before administration of norepinephrine, eventually with enlargement of the ventilatory dead space (n = 6). Under these circumstances there was a tendency for a reduction in skin oxygen saturation (−3.8–0.5%; $P = 0.066$), but no changes in SBF or skin temperature, although skin hemoglobin concentrations and skin vascular resistance index were affected (table 2).

The MCA v_{mean} increased by 6.9 cm/s. With P_{ETCO_2} correction, sc_{O_2} remained reduced by 4.2% (2.2–6.0%; fig. 2) with no change in $s_{cap}O_2$ (−3.7–4.9%).

Hypoxia

Hypoxia was associated with a reduction in skin oxygen saturation by 8.9% (6.3–11.6%; fig. 2). There was an increase in skin vascular resistance index because SBF decreased (table 2), but, on the other hand, skin hemoglobin concentrations remained unaffected.

With hypoxic exposure, Pa_{O_2} and s_aO_2 were reduced. Neither MCA v_{mean} nor CBF_{Fick} changed. Also sc_{O_2} (by 10.2%; 6.6–13.7%) and $s_{cap}O_2$ (by 7.9%; 6.4–9.4%; fig. 1) were reduced.

Discussion

The results provide, in our opinion, compelling evidence that skin oxygen saturation affects the applied spatially resolved INVOS NIRS-determined evaluation of sc_{O_2}. Whole-body heating and administration of norepinephrine provide a discrepancy between the increase respectively reduction in sc_{O_2} despite stability in $s_{cap}O_2$. On the other hand,

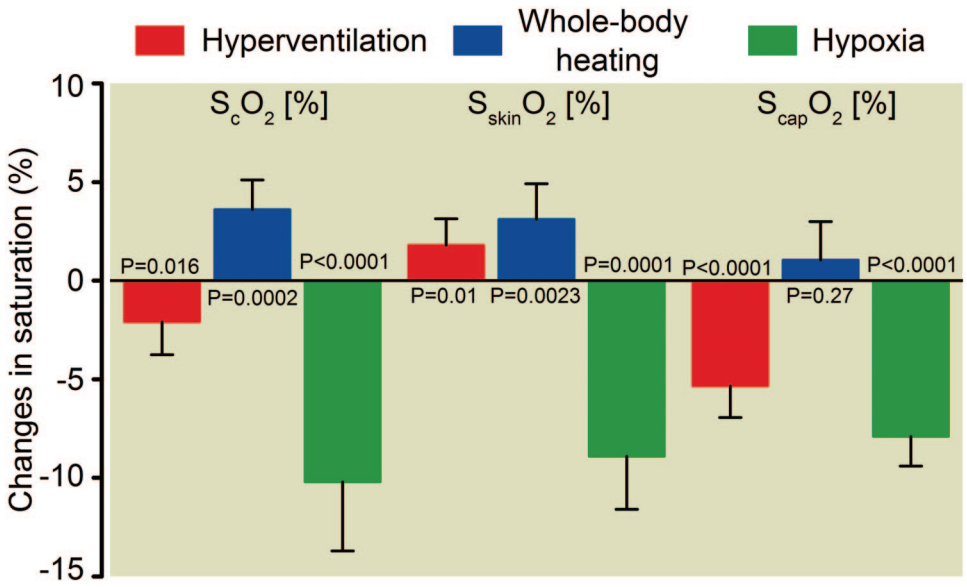

Fig. 1. Changes in cerebral oxygen saturation, skin oxygen saturation, and calculated average cerebral oxygen saturation during whole-body heating, hyperventilation, and hypoxia. *Error bars* represent 95% CI limits. *P* values for the intervention are presented. sc_{O_2} = cerebral oxygen saturation; $s_{cap}O_2$ = calculated average cerebral oxygen saturation; $s_{skin}O_2$ = skin oxygen saturation.

Table 2. Skin-derived Variables

Units of Measure	Skin Oxygen Saturation %	Total Hemoglobin of Skin AU	Oxyhemoglobin of Skin AU	Deoxyhemoglobin of the Skin AU	Vascular Resistance mmHg/cm/s	Skin Blood Flow AU	Skin Temperature °C
Control	57.0 ± 7.0	14.8 ± 8.8	8.6 ± 5.3	6.2 ± 3.9	1.5 ± 0.5	73 ± 21	33.7 ± 0.9
NE	54.5 ± 8.4*	10.7 ± 6.6*	5.8 ± 3.2*	4.9 ± 3.7*	1.9 ± 0.7‡	73 ± 26	33.7 ± 0.9
NE + CO_2	54.4 ± 7.6	11.2 ± 8.2*	6.3 ± 4.5*	5.0 ± 3.9*	1.9 ± 0.7†	73 ± 22	33.9 ± 0.8
Hyperventilation	58.3 ± 7.1*	15.5 ± 7.2	9.3 ± 4.7	6.2 ± 3.0	1.6 ± 0.6	74 ± 24	33.8 ± 0.8
WBH	60.7 ± 7.8†	14.7 ± 6.2	9.2 ± 3.9	5.5 ± 2.8	1.2 ± 0.6†	95 ± 34†	35.5 ± 0.7‡
Hypoxia	49.8 ± 8.8*	15.5 ± 8.1	8.2 ± 5.4	7.3 ± 3.2	1.8 ± 0.5†	60 ± 23†	32.7 ± 1.4‡

Skin hemodynamics with hyperventilation, whole-body heating, hypoxia (f_iO_2 = 0.12%), and administration of norepinephrine (0.15 μg · kg^{-1} · min^{-1}) with and without P_{ETCO_2} correction.

* $P < 0.05$. † $P < 0.01$. ‡ $P < 0.001$.

NE = administration of norepinephrine; NE + CO_2 = administration of norepinephrine with P_{ETCO_2}-correction; WBH = whole-body heating.

during hyperventilation and hypoxia, there were corresponding reductions in sc_{O_2} and $s_{cap}O_2$. Thus, the reduction in sc_{O_2} during administration of norepinephrine can be explained by cutaneous vasoconstriction, whereas the increase in sc_{O_2} during whole-body heating seems because of an increase in skin oxygen saturation. These observations have implications for use of NIRS clinically and for preservation of sc_{O_2} and in turn CBF with administration norepinephrine during anesthesia.

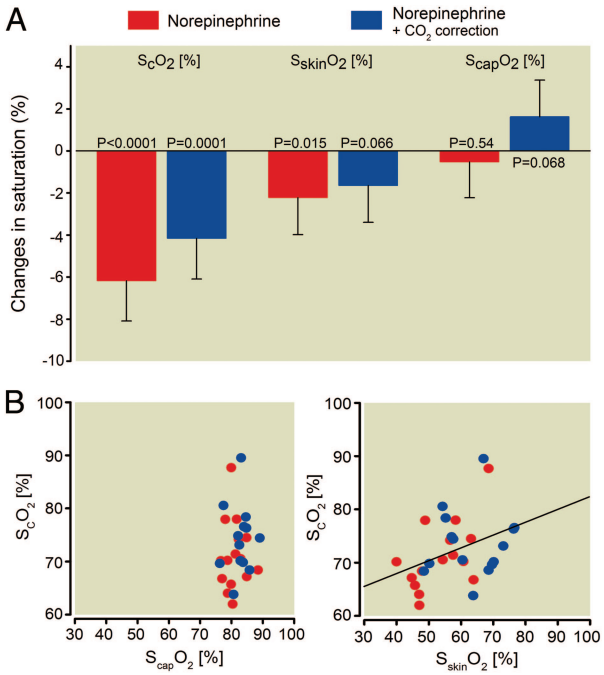

Fig. 2. (*A*) Changes in cerebral oxygen saturation, skin oxygen saturation, and calculated average cerebral oxygen saturation during administration of norepinephrine (0.15 μg · kg^{-1} · min^{-1}) with and without P_{ETCO_2} correction. *Error bars* represent 95% CI limits and *P* values for the intervention are presented. (*B*) Correlation of cerebral oxygen saturation with both calculated average cerebral oxygen saturation and skin oxygen saturation, during administration of norepinephrine with and without P_{ETCO_2} correction. sc_{O_2} = cerebral oxygen saturation; $s_{cap}O_2$ = calculated average cerebral oxygen saturation; $s_{skin}O_2$ = skin oxygen saturation.

The calculation of cerebral oxygenation from arterial and jugular bulb saturation is of importance to this study. Here, we used an approach based on cerebral oxygen extraction and defined the average cerebral blood hemoglobin oxygenation as the midway point between the arterial and jugular venous saturations.[29] Others have proposed a 3:1 ratio primarily based on anatomical evidence between arterial and venous blood for validation of NIRS.[35] The contribution ratio may be different between NIRS devices and it is unlikely that the composition of cerebral blood volume remains stable at different levels of P_{CO_2} and, consequently, CBF.[1,36] The NIRS-derived arterial-to-venous ratios are somewhat contradicted by positron emission tomography data,[37] but contribution from skin may have influenced NIRS validation of the cerebral blood volume distribution. Importantly, using a 3:1 ratio between arterial and venous blood, or $s_{jug}O_2$ alone, does not change the conclusion that skin has a significant contribution to the NIRS signal.

Vasodilation of the Skin

The penetration depth sensitivity of NIRS light is proportional to the emitter-detector separation.[24] The presented results raise the question whether a separation distance of 3 or 4 cm is enough to secure spatial resolution and thereby exclude crosstalk between sc_{O_2} and skin oxygen saturation. With whole-body heating, we obtained an increase in sc_{O_2} and skin oxygen saturation, whereas calculated $s_{cap}O_2$ remained stable (fig. 1). Thus, the increase in sc_{O_2} associated with whole-body heating can be explained by the increase in skin oxygen saturation. Nonspatially resolved NIRS is affected by skin oxygen saturation with local and whole-body heating[13] and with intradermal injections of epinephrine.[14] Here, with spatially resolved NIRS, we observed a correlation between sc_{O_2} and skin oxygen saturation during administration of norepinephrine with and without P_{ETCO_2} correction (fig. 2) and a similar correlation was observed during whole-body heating (fig. 3). In support for an influence of skin

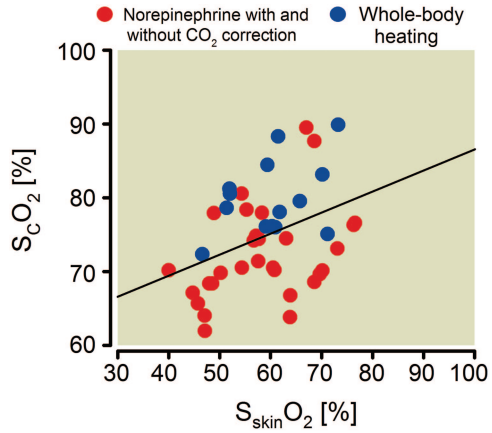

Fig. 3. Correlation of skin oxygen saturation and cerebral oxygen saturation during administration of norepinephrine with and without P_{ETCO_2} correction, represented as *red dots*, and whole-body heating presented as *blue dots*. For all data in the plot, r = 0.64 ($P < 0.0001$), with r = 0.6 ($P < 0.0001$) for administration of norepinephrine and r = 0.4 ($P = 0.15$) for whole-body heating. scO_2 = cerebral oxygen saturation; $s_{skin}O_2$ = skin oxygen saturation.

oxygen saturation on scO_2, a marked increase in SBF and reduced skin vascular resistance index were observed. Marked hyperthermia can elicit hyperventilation, but $PaCO_2$ was maintained during whole-body heating and therefore did not affect cerebrovascular resistance index and sjO_2 as previously described.[1] Core temperature was not recorded, but the results show no changes in $PaCO_2$, MCA v_{mean}, or CBF_{Fick}, typically seen during whole-body heating.[9]

Vasoconstriction of the Skin

Previous studies suggest that administration of vasopressors exert a negative impact on scO_2.[5–7] It is debated whether the reduction in scO_2 is because of a decrease in cardiac output,[38] sympathetically mediated cerebral vasoconstriction, or changes in SBF.[34] It is less ambiguous how α-adrenergic drugs affect the microcirculation of the skin.[39] The present results demonstrate a decrease in skin oxygen saturation with administration of norepinephrine (fig. 2) and lower skin hemoglobin concentrations and increased skin vascular resistance index. At the same time, scO_2 decreased whereas calculated $s_{cap}O_2$ was unaffected, suggesting that cutaneous vasoconstriction affects the NIRS-determined scO_2. In support, when P_{ETCO_2} was maintained, the reductions in scO_2 and skin oxygen saturation remained and the reduction in scO_2 during administration of norepinephrine could illustrate the influence of skin oxygen saturation considering that $s_{cap}O_2$ was stable.

Administration of phenylephrine provokes a marked reduction in scO_2 despite unaffected internal carotid artery flow, PaO_2 and $PaCO_2$.[34] We acknowledge that a decrease in scO_2 with administration of norepinephrine could be because of an alteration in the arterial and venous contributions to the NIRS signal, but also, cutaneous vasoconstriction could be responsible for the reduction in scO_2. Administration of ephedrine, on the other hand, does not affect scO_2.[5–7] One explanation for this discrepancy could be that ephedrine does not have the same vasoconstrictive effects on smooth muscles in skin vasculature as norepinephrine. Reduction in cardiac output has a negative impact on scO_2,[40] but the present results suggest that the reduction in scO_2 is explained by a reduction in skin oxygen saturation. The stability of MCA v_{mean} and CBF_{Fick} also emphasize that cerebral blood flow is not challenged, which would have been the case if cardiac output was lowered.[40] It remains unknown to what extent the cerebral vasculature is influenced by sympathetic innervation, but the results do not support sympathetic vasoconstriction in brain (table 1).

Hypoxia and Hypocapnia

With systemic hypoxic exposure, $s_{cap}O_2$ was reduced by 7.9% and scO_2 by 10.2% ($P < 0.0001$). Therefore, it seems that NIRS estimates brain oxygen saturation correctly during systemic hypoxic exposure. The influence of the skin oxygen saturation is minimal with hypoxia, but we cannot exclude that the 2.3% discrepancy between scO_2 and $s_{cap}O_2$ can be explained by the 8.9% reduction of skin oxygen saturation ($P = 0.03$) because of cutaneous vasoconstriction (table 2). The threshold for hypoxemia-induced arterial dilatation was not reached,[41] but we cannot exclude cerebral vasodilatation because of hypoxic exposure. On the other hand, such vasodilation was likely counterbalanced by hypocapnia, because MCV v_{mean} did not change significantly (table 1).

Because of the higher oxygen pressure during hyperventilation, skin oxygen saturation increased, whereas $s_{cap}O_2$ and scO_2 decreased (fig. 1). The inverse relationship between scO_2 and skin oxygen saturation with hyperventilation could explain why scO_2 underestimates $s_{cap}O_2$ by 3.2%, however, systematic errors because of a low signal-noise ratio cannot be excluded. These findings support that $PaCO_2$ has an influence on cerebral oxygen saturation as assessed by NIRS[11] and more so than the influence of the skin oxygen saturation. Regardless of the crosstalk between skin oxygen saturation and scO_2, INVOS is sensitive to changes in cerebral oxygen saturation during hyperventilation and systemic hypoxic exposure.

Perspective

Despite the influence of SBF for the NIRS signal, it remains useful for perioperative optimizing to improve patient outcome after anesthesia,[2,25] although administration of α-agonists as vasopressors may confound interpretation of NIRS. Further studies are needed to evaluate whether difference in emitter-detector separation of more than 3 and 4 cm can avoid crosstalk between skin oxygen saturation and spatially resolved scO_2. Alternatively, different algorithms for the analysis of NIRS data are required to suppress skin artifacts. In a multiple regression analysis, skin oxygenation contributes

approximately 30% to the NIRS signal; however, further investigations are needed to quantify in details the contribution from the different components beneath the NIRS sensor. Furthermore, it is needed to evaluate whether administration of norepinephrine is associated with reduction in scO_2 in situations with low cardiac out or hypotension.

Conclusion

The results suggest that the reduced INVOS NIRS-determined evaluation of scO_2 observed with administration of norepinephrine is because of skin vasoconstriction rather than cerebral deoxygenation. Thus, in situations with administration of norepinephrine and whole-body heating, an emitter-detector separation of 3 or 4 cm seems not to be large enough to avoid crosstalk between skin oxygen saturation and the INVOS NIRS-determined scO_2, and further technical measures to eliminate the skin contribution should be considered. Nevertheless, the results confirm that spatial resolved NIRS is able to detect cerebral deoxygenation associated with hyperventilation and systemic hypoxic exposure.

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